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AFFYMETRIX, INC
3380 CENTRAL EXPRESSWAY
SANTA CLARA, CA 95051

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FREDMAN, JEFFREY NORMAN	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/827,383
Filing Date: April 04, 2001
Appellant(s): MITTMANN ET AL.

Sandra Wells
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 24, 2005.

500

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of the claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is correct.

(7) Prior Art of Record

Dujon et al. "The Yeast Genome Project: What did we learn". Trends in Genetics, Vol. 12, No. 7 (July 1996), pp. 263-270.

(8) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 7, 15-19 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a set of nucleic acids tags with at least 1000 sequences whose sequences comprise SEQ ID NO: 1-2050, with SEQ ID Nos: 1-10 being selected.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the nucleic acids. One cited utility identified in the specification is to analyze genomic DNA (see page 10, for example). This utility is credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the nucleic acid. No well established utilities for these specific SEQ ID Nos: 1-10 are identified in either the specification or in the cited prior art.

Substantial utility

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. Here, there is no evidence of any substantial utility. No substantial use for a set of sequences comprising SEQ ID NOs: 1-10 is found in the specification nor is there any use for the method or system involving SEQ ID NO: 1.

As noted in the utility guidelines, methods of treating unspecified diseases, basic research on a product to identify properties, intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials). If there were evidence of the association of SEQ ID NO: 1 with any disease state, with a protein activity or with some other biological phenotype, this evidence might be considered regarding a substantial utility. However, no such evidence is found. At best, the utilities of analyzing genomic DNA are indicative that SEQ ID NOs: 1-10 are intermediate products which lack substantial utility.

In the Supreme Court case of *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), a novel compound which was structurally analogous to other compounds that were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a set of polynucleotides with no known function. The specification does not teach the function of any of the nucleic acids to which these sequences hybridize. The function of these nucleic acids is as yet undetermined with no known biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the nucleic acid of the instant application was, as of the filing date, useful for any specific assay or therapeutic use. Until some actual and specific significance can be attributed to the nucleic acid, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. Following both the Utility Guidelines and the direction of the Supreme Court of the United States in Brenner, there is no specific benefit in using a set of these specific sequences. Thus, there is no immediately substantial or "real world" utility as of the filing date.

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is clearly no specific utility. To the extent that the nucleic acid and polymorphisms in SEQ ID NO: 1-10 can be used in genomic analysis assays, this utility is not at all specific to SEQ ID NO: 1-10. Literally any sequence would function in a genome analysis assay as described in the specification. As the utility guideline

training materials note on page 5-6 regarding specific utility that "a claim to a polynucleotide whose use is disclosed simply as a 'gene probe' or 'chromosome marker' would not be considered to be *specific* in the absence of a disclosure of a specific DNA target (italics in original)". Here, there is no disclosure of any specific use of SEQ ID NO: 1-10 that is not shared with any other sequence.

Further, the sequences are not even species or chromosome specific, based upon the sequence search. As the attached search of SEQ ID NO: 3 in Genbank demonstrates, result 3 shows an 90% match (local similarity) to a sequence in chromosome 14 of humans while result 13 shows an 89.5% match (local similarity) to human chromosome 8. Further, the remaining results show similarity to Pseudomonas, Lotus, Rats and Rice with equivalent levels of local similarity. Similar results exist for the other 9 probes. So the sequences claimed lack 100% specificity to any particular organism in Genbank, and the specification lacks any discussion of the target for these oligonucleotides. Consequently, there is no specific target for any of the claimed sequences. With regard to the utility analysis, the current situation directly tracks Example 9 of the utility guidelines, where an unknown nucleic acid fragment of entirely unknown function was characterized as lacking utility.

Finally, there appears to be no element which is unique to the selected sequences. That is, the ability of the array to be used in SNP-IT™ assays, for example, is not sequence dependent. That is, there is nothing specific to the 2050 sequences of the current claim which distinguish these sequences from a different set of 2050 sequences or from any set of 2050 unrelated sequences.

Therefore, a set of nucleic acids comprising SEQ ID NO: 1-10 has no specific utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 7, 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention

The current claims drawn to a set of nucleic acids tags with at least 1000 sequences whose sequences comprise SEQ ID NO: 1-2050, with SEQ ID Nos: 1-10 being selected. The nature of this invention is in nucleic acid analysis of a particular sequence with no other associated information. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Breadth of the claims

The claims are drawn to a set of nucleic acids comprising at least 1000 sequences from SEQ ID Nos: 1-2050, and for which SEQ ID Nos: 1-10 were selected.

Amount of Guidance in the Specification

The specification discloses the entire sequence of SEQ ID NOs: 1-10, but identifies no particular use for the sequence. In particular, the specification lacks any discussion of the target of SEQ ID NOS: 1-10, or of any of the 2040 other sequences. As noted in the utility rejection above, this utility is not found to be substantial nor specific and consequently, the specification provides NO guidance regarding how to use SEQ ID NO: 1. The general guidance that the method is useful in methods of genomic analysis fails to provide the specific details necessary to apply sequences whose targets are unknown to such genomic analysis.

Working Examples

There are working examples in which the sequences are hybridized. However, there are no working examples in which SEQ ID NOs: 1-10, or indeed any of the 2040 other sequences, are used in any assay for detection or diagnosis of any disease or any other related utility. No real world use or particular use is given for these sequences.

Amount of Guidance in Prior Art

As noted in the utility rejection above, the prior art provides no guidance with regard to the particular function of SEQ ID NOs: 1-10.

Skill in the Art

While no evidence is adduced, the examiner believes the skill in the art would be considered high.

Predictability of the Art

The art in biotechnology, as relates to the association of diseases with particular genes, is highly unpredictable. The claimed sequences currently appear to represent orphan genes, since no matches were identified in a sequence search. Regarding such Orphan genes, Dujon (Trends in Genetics (1996) 12(7):263-270) notes that the most striking result of yeast sequencing is that "a significant proportion of yeast genes are orphans of unpredictable function (abstract)". Dujon further states "We have no clue to which direction to search and, even worse, when considering the experiments that could be done on orphans, we rapidly find ourselves intellectually embedded in the schemes of the past (page 2169, column 2)." Thus, it is extremely unpredictable what to do with an orphan gene such as SEQ ID NOs: 1-10 in the absence of any defined utility.

Further, as noted above, the sequences are not even species or chromosome specific, based upon the sequence search. As the attached search of SEQ ID NO: 3 in Genbank demonstrates, result 3 shows an 90% match (local similarity) to a sequence in chromosome 14 of humans while result 13 shows an 89.5% match (local similarity) to human chromosome 8. Further, the remaining results show similarity to Pseudomonas, Lotus, Rats and Rice with equivalent levels of local similarity. Similar results exist for the other 9 probes. So the sequences claimed lack 100% specificity to any particular organism in Genbank, and the specification lacks any discussion of the target for these oligonucleotides. Consequently, there is no specific target for any of the claimed sequences. In the absence of any target, it is entirely unpredictable how these sequences would function even in some sort of genomic analysis method. SEQ ID NO: 3, for example, would crosshybridize to both chromosomes 8 and 14 and would not give significant information regarding the presence or absence of any particular human,

animal or plant sequence in a sample, since the sequence would hybridize about equally well to human, rat, rice and lotus, among other species.

Quantity of Experimentation

An immense amount of experimentation would be required in order to define whether any of these nucleic acids are associated with any particular disease state or other specific and substantial use. For example, in order to acquire statistically significant evidence of an association with a disease or other utility, one of the possible targets such as human patients, experimental rats, or rice and lotus plants in each of the many hundreds of different possible disease states would need to be subjected to collection of samples for analysis of their DNA, followed by analysis and the inventive efforts of determining if any association exists. This is a very large quantity of experimentation.

Determination

In view of the unpredictable nature of the invention, the absence of any guidance in the specification for a substantial and specific use, the absence of any working examples in the specification, the negative teachings in the prior art, the extreme unpredictability of the invention, and the large amount of experimentation necessary balanced against the high level of skill in the art and the relatively narrow breadth of the claims, it is concluded that undue experimentation would be required to use this invention as claimed.

(9) Response to Argument

Introduction

> "Merely stating that a nucleotide sequence could be used as a probe in a microarray is a general utility that does not distinguish that particular sequence from *any other sequence.* Using a nucleic acid sequence of unknown function as a probe on a microarray does not provide a specific utility for that sequence (emphasis in original)."

This quote from page 16 of the Affymetrix Amicus brief in support of the Board of Patent Appeals and Interference decision in In re Fisher (see http://patentlaw.typepad.com/patent/files/affymetrix_amicus_brief.pdf) captures the essence of the utility argument. Using a sequence on a microarray does not provide a specific utility for the sequences on the microarray.

The subject matter of this application is directed towards a set of nucleic acid tag probes comprising at least 1000 nucleic acid sequences chosen from the group consisting of SEQ ID NOS: 1-2000 from which the Appellant elected 10 sequences, SEQ ID Nos: 1-10. Just as ESTs represent a small selection of the entire genomic DNA, selected by filtering out sequences which are not capable of being expressed, sequences which are capable of expression but not in the sample being analyzed, and sequences which lack the ability to be primed by the reverse transcriptase primers, the claimed nucleic acid tag probes were filtered. As the specification states at pages 8-9,

> "An initial set of 2200 20mer sequences was selected with closely matched melting temperatures. A further filter based on rules such as those described in US Provisional Patent Application 60/176,520 was applied to optimized and standardize the hybridization characteristics of the set. Finally, sequences were removed if they were identical or nearly identical to each other or to sequences in

> the public databases. This reduced the pool of candidate sequences to 2200. The hybridization performance of the entire set of 2200 candidate sequences was evaluated. Labeled oligonucleotides complementary to the candidate sequences were synthesized and hybridized to an array containing probes designed to analyze the performance of all 2200 candidate sequences..... A line was fitted to select the 2050 sequences with the highest discrimination and signal intensity. These 2050 sequences are SEQ ID Nos. 1-2050."

The specification thus teaches that Appellant selected 2200 20mer sequences with similar melting properties and filtered 150 out of those 2200, resulting in a claim for the remaining 2050 20 mer tag sequences. The specification provides a list of asserted utilities for the invention at pages 9 and 10, teaching the use of SEQ ID Nos: 1-2050 as tags.

Legal standard for Utility

The starting point for determining whether a set of 1000 nucleic acid molecules selected from the group consisting of SEQ ID NO: 1 through SEQ ID NO: 2050 possesses utility under 35 U.S.C. § 101 is Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). As set forth in Brenner, at 534-35, 148 USPQ at 695,

> the basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until [an invention] is refined and developed to this point--where specific benefit exists in currently available form--there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

In considering the issues presented in this appeal, special attention must be paid to the Brenner court's statement that a patent should issue only when an invention possesses "substantial utility," i.e., "where a specific benefit exists in currently available form."

Whether a claimed invention is useful under 35 U.S.C. § 101 is a question of fact. Cross v. Iizuka, 753 F.2d 1040, 1044 n.7, 224 USPQ 739, 742 n.7 (Fed. Cir. 1985).

The utility issue raised in the current case differs significantly on the facts from previously decided precedent. As Appellant recognized, the decision by the Board of Patent Appeals and Interferences (BPAI) in Ex parte Fisher provides an excellent summary of utility caselaw. However, another decision by the BPAI, Ex Parte Turner, provides a significant discussion of the microarray utilities. In Turner, the BPAI notes,

> "Finally, adopting the per se rule that Appellants seek—that any expressed human gene has utility because it can be used in a DNA chip—would mean that almost any naturally occurring nucleic acid would be patentable. Appellants' reasoning does not depend on the biological function of the protein encoded by the claimed nucleic acids, and so would apparently apply to any expressed human gene, as well as fragments of them."

This legal analysis would apply with greater force in the current case. If the current Appellant is correct, then any nucleic acid whatsoever has utility as a tag, irrespective of whether there is any specific or substantial utility known for the sequence. Further, since every protein can be detected with specific antibodies directed towards that protein, which could also be placed upon an array and the protein used as a tag, Appellant's argument would lead to the inevitable conclusion that every biological molecule has utility as a tag on a microarray. This conclusion would be based solely upon the nature of biological information and the capacity of biological molecules to interact specifically with one another, irrespective of whether there was any "specific benefit" of the molecule relative to other molecules in the same class.

The BPAI determination in Turner supports this analysis, where the BPAI noted,

> "Under Appellants' rule, then, any polynucleotide from an expressed gene would be patentable if it was adequately described in the specification and was not disclosed or suggested in the prior art. This standard, however, is not the one set by Congress, which requires that a patentable invention also be useful and fully enabled, nor is it the standard that has been consistently applied by the courts. In addition, the flood of DNA patents that would result from adoption of Appellants' rule could doom the potential contribution of microarrays to biological research. Appellants argue that "[g]iven the widespread utility of such 'gene chip' methods using public domain gene sequence information, there can be little doubt that the use of the presently described novel sequences would have great utility in such DNA chip applications." Appeal Brief, page 15. "[T]here is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format." Id. The practical effect of Appellants' utility standard, however, would be that making a microarray with 1000 genes represented on it would require investigating each of the DNA sequences (and subsequences) on the gene chip to ensure that it was not the subject of someone else's patent. For each of the DNAs that was the subject of someone else's patent claim, a license would have to be negotiated – potentially thousands of such negotiations for the finished product. These transaction costs would have to be incurred for each new product that an aspiring gene chip manufacturer wished to market. The industry gridlock likely to result has been termed a "tragedy of the anticommons.""

The difference in the facts between the current case and Turner and Fisher is that Turner and Fisher deal with the limited subset of all possible nucleic acid sequences which are expressed sequence tags. The ESTs in Turner and Fisher represent nucleic acids which actually exist in particular biological organisms. The current claims, while drawn to specific SEQ ID NOs, are in fact representative of a broader class that represents potentially every possible sequence.

Specific Utility standard applied to the current Facts

It is important to analyze this legal framework provided by the Brenner court and subsequent decisions of the Federal Circuit in the context of nucleic acids as both physical products and informational molecules. When the Board analyzed the ESTs in Fisher and Turner, the Board recognized that an invention can have a utility that is shared by other compounds or compositions. The Board also noted, however, that not every utility will satisfy § 101, even if the utility is shared by a class of inventions. The Board concluded that while a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy § 101.

The factual situation in the current case support the determination that there is a lack of specific utility. There are, at most, about three billion different 20 mers that can exist in the human genome (if every 20 bases is different from every other 20 bases). This represents only 0.02% of all possible 20 mers (4^{20} or about 10^{12}). If these "human genome specific" 20 mers are excluded, STILL about 10^{12} different 20 mers would remain and would be capable of functioning as tags in Appellants invention. However, even almost all of the excluded "human genome specific" 20 mers would be capable of being specific if the genome of interest was Escherichi coli. Finally, those few 20 mer tags found in both humans and E. coli, while probably capable of use in some other organism, could certainly be used in the utility cited by Appellant, as tags for explosives.

The current claims are drawn to specific nucleic acid sequences, specific SEQ ID Nos, and not to nucleic acids in general. Appellant is attempting to obtain patents on sets of specific DNA sequences, such as taaactagcattgagcccac (SEQ ID NO: 1) and not

on nucleic acids in general. Appellant has shown no specific utility that is unique to SEQ ID NO: 1, other than having been filtered as not being precisely identical to any known genomic sequence. Out of the 1,099,511,627,776 different 20 mers which can be made, the vast majority will meet Appellant's filtering requirement.

Appellants own argument supports this conclusion. When Appellant argues that nucleic acids can be used as tags in explosives, it is clear that any nucleic acid can serve to tag the explosive since there is no expectation of contaminating targets. The complements of these explosive tags could be placed on a microarray and used to detect the nucleic acid tags in the explosives. Therefore, Appellant's argument supports the conclusion that any nucleic acid whatsoever can serve as a tag. This is the exact opposite of the requirement in the Utility guidelines that a specific utility exist.

Contrary to Appellant's argument, the utility of a tag is more similar to the example in Fisher where ibuprofen is used as a weight, and the utility is not that of an analgesic. That is, when a nucleic acid is used solely as a tag, there is nothing specific to the particular sequence of the nucleic acid which renders it useful, but rather, it is the generic ability of all nucleic acids to hybridize to their complement which renders the nucleic acid useful. This is not a utility that is specific to the sequences of the nucleic acids of SEQ ID NOs: 1-2050 that are currently being claimed but rather is a utility that is general to all nucleic acids. Indeed, the ability to bind specifically is a utility that can be found in any biological macromolecule. There are specific interactions for individual nucleic acids by hybridization, for proteins by binding, for carbohydrates and lipids by binding and for interactions between these class such as DNA binding proteins. All of

these biological macromolecules could be placed on arrays and used as tags to bind to their specific partners. Thus, if Appellant's view is accepted, every biological macromolecule has a specific utility. Many, if not most, of these macromolecules will have no "specific benefit in currently available form" other than their ability to bind specifically. While further research may eventually show that a particular nucleic acid is useful diagnostically to detect overexpression in cancer, an allele associated with Alzheimers or capable of expressing a commercially valuable ligase enzyme, until such time as that research is performed, and the specific utility for that particular nucleic acid established, there is no "specific benefit in currently available form".

When Appellant points to specific uses of tag arrays in the prior art, specifically citing Fan et al, Shoemaker et al, and Hardenbol et al, the utility of those inventions did not rely upon the specific sequences of the tags on the microarray. Any tags which provided the needed specificity would have sufficed for these uses. There was nothing specific in the selected tag population that provided a "specific benefit". The benefit in this case is generic to all possible tag sequences.

The Affymetrix amicus brief in In re Fisher comments "Any nucleic acid sequence that does not have a known function, whether it is an EST or full-length RNA molecule, does not have patentable utility (emphasis in original)." In the current case, there is no known function for the claimed nucleic acid sequences other than the generic function of serving as a tag. Based upon the "specific benefit" required by Brenner as analyzed under the framework in Fisher and Turner, there is no "specific benefit" for SEQ ID NOs: 1-10.

In conclusion, the words of the Affymetrix Amicus brief best convey the underlying reason why the current claims lack patentable utility under the specific utility prong. "Merely stating that a nucleotide sequence could be used as a probe in a microarray is a general utility that does not distinguish that particular sequence from *any other sequence.* Using a nucleic acid sequence of unknown function as a probe on a microarray does not provide a specific utility for that sequence."

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Jeffrey Fredman
Primary Examiner
Art Unit 1637
7/14/05

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Conferees

Michael Woodward
TQAS

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Gary Benzion
SPE 1637

AFFYMETRIX, INC
3380 CENTRAL EXPRESSWAY
SANTA CLARA, CA 95051

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600